75. The nucleic acid molecule of claim 74 wherein said encoded discrete peptide binds to more than three of said HLA molecules.

76. The nucleic acid molecule of claim 71 wherein said nucleotide sequence further encodes a second discrete peptide consisting of 8-11 amino acids which is a CTL epitope.

77. The nucleic acid molecule of any of claims 71-76 wherein the encoded first peptide is derived from an HIV antigen, an HBV antigen, an HCV antigen, an HPV antigen, or a malaria antigen.

REMARKS

The claims have been amended to make clear that they are supported by the specification and to focus on the nature of the invention. The invention resides in the discovery that a large proportion of peptides containing a particular motif is successful in binding HLA molecules encoded by a multiplicity of alleles. The specification as filed clearly supports the claimed subject matter. For example, page 23 of the specification states that the peptides of the invention can be expressed by attenuated viral hosts such as vaccinia or smallpox, thus supporting the concept of a nucleic acid molecule encoding the peptides. Further, page 17 of the specification as filed, lines 20-27 state that recombinant DNA technology can be employed to produce the peptides of the invention. As to the peptide consisting of 8-11 amino acids, this is supported by the definition of motif on page 3, lines 23-26. Applicants note that the Examiner has pointed to page 2, lines 23-24, as assertedly limiting the immunogenic peptides to those of 9-10 residues; however, it is believed that 8-11 is equivalent to "about" 9-10 residues. The 9-10 residue embodiments are merely preferred as noted on page 3, lines 10-12.

All of this is also completely supported in U.S. Serial No. 08/278,634 filed 21 July 1994 and U.S. Serial No. 08/334,824 filed 23 November 1994 which were incorporated into the

present application by reference. Page 3 of the '824 application, lines 12-14, point out that the relevant motif is in a peptide of defined length of 8-11 amino acids; see also line 4. Page 17 of that application notes, as does the present application, that the peptides can be produced by recombinant DNA technology. Page 23 of that application, at lines 6-9, describes use of nucleic acids as vaccines. And, importantly, on page 33 of that application, Example 3 demonstrates that the claimed motif in the context of an 8-11 amino acid peptide has a proline at position 2 and a hydrophobic amino acid at the C-terminus. The specific amino acids set forth in claim 72 as embodiments of the C-terminus are supported in Table 6. Table 6 also supports the required ability of the peptide to bind to the specified alleles: B3503, B0701, B1401, B5101, B5301 and CW0602; ability to bind to B3501 and B3502 as well as B5401 is shown in Table 12.

As stated on page 3, line 20 et seq., in the '824 application, the "supermotif" represented by the pattern of amino acids set forth in the claims characterizes peptides that have a high probability of binding to at least two HLA molecules encoded by the alleles listed in proposed claim 71. Essentially, this motif represents a set of the motifs characteristic of these alleles individually which is permissive with respect to the remaining amino acids in the molecule as they affect binding ability. Thus, when the supermotif is present, the probability of the peptide binding at least two, or preferably at least three, or preferably more than three alleles is enhanced. This is particularly true where a set of motifs is shared with all the members of the family. As shown in Table 6 in the '634 application, the supermotif binding the individual allele B0701 contains at the C-terminus any of L, I, V, Y, F or W as does that for the B5301 and CW0602 alleles. However, all five alleles shown in this family in Table 6 permit L,I, or V at the C-terminus. Thus, peptides with the supermotif set forth in claim 73 are especially likely to bind to a plurality of alleles.

Thus, the claims as currently presented are fully supported not only by the present application but by the priority documents having effective dates of 21 July 1994 and 23 November 1994.

Priority

As stated above, the present application claims priority to a number of preceding applications. The specification has been corrected accordingly. The Office points out that the parent application does not disclose the elected species; however, the elected species is no longer being claimed specifically, but only as a member of a genus. The genus is fully supported by the ancestor applications.

The New Matter Rejection

It is believed that most of this rejection has been obviated by the amendment to the claims. The objection set forth in paragraph 1 has been addressed above. The words "structural motif" and the "proviso that the immunogenic peptide does not comprise an entire native antigen" and a "non-naturally occurring peptide" and "an antigen derived from a pathogenic agent" no longer appear in the claims. Neither do the words "*in vitro* or *in vivo*" or "wherein the immunogenic peptide is more than about 11 amino acid residues in length" appear in the claims. The restriction on binding IC_{50} values is supported, for example, in Example 8 of the application 08/334,824 from which priority is claimed and which was incorporated by reference at page 49, line 28.

The Rejection Under 35 U.S.C. § 112, First Paragraph (Enablement/Utility)

The Office argues that additional amino acid sequence over and above that which constitutes the epitope having the required motif would interfere with the binding of the peptide to the HLA molecule. It is believed that this aspect of the rejection is obviated by the present claims which are restricted to nucleic acid molecules encoding discrete peptides of 8-11 amino acids in length.

The Office further points out that there is no "guarantee" that a peptide which binds to an HLA molecule would actually be immunogenic. Applicants agree there is no guarantee. However, what applicants have done is to enhance the likelihood of immunogenicity in any

candidate peptide in a large segment of the population by requiring that the appropriate structural motif be present, and assuring that the encoded peptide binds to at least two HLA molecules encoded by two different alleles. The peptides of the invention are useful as candidate vaccine peptides; there is no necessity for a guarantee that each and every one of these candidates will succeed. Relevant wording has been removed from the claim language.

The Rejection Under 35 U.S.C. § 112, Second Paragraph

This rejection is also obviated by the amended claims which no longer contain the objected-to terminology.

The Rejections Under 35 U.S.C. § 103

The claims were rejected over the combination of Sidney, *et al., J. Immunol.* (1996) 157:3480-3490 in view of WO93/03764 and optionally in further view of U.S. patent 5,580,859. The rejections require the disclosure of the primary reference Sidney, *et al.* Since the claims as presently proposed are entitled to the priority of 1994, Sidney is no longer citable. Accordingly, the pending claims are free of this rejection.

CONCLUSION

The claims have been amended to confine them to nucleic acids which contain nucleotide sequences that encode discrete peptides of 8-11 amino acids having the disclosed supermotif. The peptides thus encoded are viable candidates for immunogenic peptides in a substantial portion of the population by virtue of the ability of a large proportion of these peptides to bind to HLA molecules encoded by a multiplicity of alleles. The claims are entitled to the priority of the originally filed application, removing the required Sidney, *et al.*, paper as a citable document. It will be noted that the Sidney, *et al.*, paper is corresponding publication of the supermotif described in this series of applications. It is thus believed that claims 71-77 are in a position for allowance and passage of these claims to issue is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 399632805000. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

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